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Efficacy and Safety of Upadacitinib Treatment in Adolescents With Moderate-to-Severe Atopic Dermatitis

Analysis of the Measure Up 1, Measure Up 2, and AD Up Randomized Clinical Trials

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Key Points

Question

Does upadacitinib safely improve moderate-to-severe atopic dermatitis in adolescents?

Findings

Among 552 adolescents participating in 3 randomized clinical trials, upadacitinib administered once daily was generally well tolerated through 16 weeks. A greater proportion of adolescents treated with upadacitinib achieved end points associated with clinically important improvements in signs and symptoms of atopic dermatitis compared with placebo, and the most common dose-related adverse effects were acne and elevations in creatine phosphokinase levels.

Meaning

In adolescents with moderate-to-severe atopic dermatitis, the safety and efficacy of upadacitinib were similar to that reported in adults, supporting a favorable benefit-risk profile for upadacitinib in adolescents aged 12 to 17 years.

Abstract

Importance

Atopic dermatitis onset usually occurs in childhood. Persistence of disease into adolescence and adulthood is common. It is important to evaluate new treatment options in adolescents because of the high unmet need in this population.

Objective

To assess the efficacy and safety of upadacitinib to treat moderate-to-severe atopic dermatitis in adolescents.

Design, Setting, and Participants

Prespecified analysis of adolescents enrolled in 3 randomized, double-blind, placebo-controlled phase 3 clinical trials in more than 20 countries across Europe, North and South America, Oceania, the Middle East, and the Asia-Pacific region from July 2018 through December 2020. Participants were adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis. Data analysis was performed from April to August 2021.

Interventions

Patients were randomized (1:1:1) to once-daily oral upadacitinib 15 mg, upadacitinib 30 mg, or placebo alone (Measure Up 1 and Measure Up 2) or with topical corticosteroids (AD Up).

Main Outcomes and Measures

Safety and efficacy, including at least a 75% improvement in the Eczema Area and Severity Index from baseline and validated Investigator Global Assessment for Atopic Dermatitis score of 0 (clear) or 1 (almost clear) at week 16 (coprimary end points).

Results

A total of 552 adolescents (290 female; 262 male) were randomized. Mean (SD) age was 15.4 (1.8), 15.5 (1.7), and 15.3 (1.8) years for adolescents in Measure Up 1, Measure Up 2, and AD Up, respectively. In Measure Up 1, Measure Up 2, and AD Up, respectively, a greater proportion of adolescents (% [95% CI]) achieved at least 75% improvement in the Eczema Area and Severity Index at week 16 with upadacitinib 15 mg (73% [63%-84%], 69% [57%-81%], 63% [51%-76%]), and upadacitinib 30 mg (78% [68%-88%], 73% [62%-85%], 84% [75%-94%]), than with placebo (12% [4%-20%], 13% [5%-22%], 30% [19%-42%]; nominal $P < .001$ for all comparisons vs placebo). Similarly, a greater proportion of adolescents treated with upadacitinib achieved a validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1 at week 16 and improvements in quality of life with upadacitinib than with placebo. Upadacitinib was generally well tolerated in adolescents. Acne was the most common adverse event, and all acne events were mild or moderate.

Conclusions and Relevance

In this analysis of 3 randomized clinical trials, upadacitinib was an effective treatment for adolescents with moderate-to-severe atopic dermatitis, with an acceptable safety profile.

Trial Registration

ClinicalTrials.gov Identifiers: NCT03569293 (Measure Up 1), NCT03607422 (Measure Up 2), and NCT03568318 (AD Up)

Introduction

Atopic dermatitis (AD) is a chronic, recurrent, immune-mediated inflammatory skin disease characterized by eczematous morphology and intense itch.[1,2] Onset of AD typically occurs early in life,[2,3] with a lifetime prevalence of 14.8% in adolescents aged 12 to 17 years.[4] Atopic dermatitis in adolescents can be associated with low self-esteem, mood disturbances, antidepressant use, poor sleep quality, school absenteeism, and impaired overall health-related quality of life.[2,5,6]

The US and European guidelines make few distinctions between the diagnosis, assessment, and treatment of AD in adolescents and adults.[7,8,9,10] The objective of this interim analysis was to assess the safety and efficacy of upadacitinib[11,12] alone or in combination with topical corticosteroids (TCS) in adolescents aged 12 to 17 years with moderate-to-severe AD enrolled in the Measure Up 1, Measure Up 2, and AD Up studies.[13,14]

Methods

Study Design and Patients

Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD Up (NCT03568318) are multicenter, randomized, parallel, double-blind, placebo-controlled, phase 3 clinical trials, with a completed double-blind period of 16 weeks[13,14] and an ongoing blinded extension period of up to 260 weeks, conducted in countries across Europe, North and South America, Oceania, the Middle East, and the Asia-Pacific region. Eligible patients were adults aged 18 to 75 years or adolescents aged 12 to 17 years with body weight 40 kg or greater (for study design, see eFigure 1 in Supplement 1). Independent ethics committees or institutional review boards at each site approved the protocols, informed consent forms, and recruitment materials before enrollment. Patients or their parents/legal guardians provided written informed consent.

Each clinical trial contains a main study portion that includes both adults and adolescents, and an adolescent substudy portion. Patients were randomized (1:1:1) to once-daily oral upadacitinib 15 mg, upadacitinib 30 mg, or placebo alone (Measure Up 1 and Measure Up 2) or with concomitant TCS (AD Up) for 16 weeks. Randomization in the main studies was stratified by disease severity, geographic region, and age (adolescent [12-17 years] and adult [≥18 years]). Randomization for the adolescent substudies was stratified by disease severity and geographic region. Because the studies were conducted across multiple jurisdictions with different TCS product availability, it was not possible to have a single TCS preparation for every potency across study sites. In AD Up, choice of TCS was per investigator discretion. For nonsensitive areas, the protocol recommended a step-down regimen for active areas starting with medium-potency TCS applied daily for a maximum of 3 consecutive weeks, followed by low-potency TCS or topical calcineurin inhibitors applied daily for 7 days. For sensitive areas, the protocol recommended starting with low-potency TCS or topical calcineurin inhibitors applied daily.[13,14] Rescue therapy was permitted after week 4 based on persistent disease activity (Eczema Area and Severity Index [EASI] <50). Adolescents in each substudy were not included in the previously reported main study analyses.[13,14] On completion of main study enrollment, the adolescent substudy continued until 180 adolescents were enrolled (main plus substudy) in each of the 3 studies. Randomization was performed using an interactive response technology system according to a schedule generated by AbbVie randomization specialists. Study sites and patients remained blinded to treatment assignments for study duration; the sponsor was unblinded to treatment when all patients completed the 16-week double-blind period of either the main studies or adolescent substudies. Study drug was dispensed in identical containers with a unique kit number to maintain blinding.

The prespecified adolescent analyses included all adolescents enrolled in the main study and adolescent substudy. The planned sample size of 180 adolescents was determined to ensure a total of 225 patients per dose across the 3 studies. Because concomitant TCS use and rescue medication criteria were different across studies, data are presented for each study separately. A parallel planned analysis of the adult population for each study was also conducted; results are summarized in eTables 1 and 2 in Supplement 1. Trial protocols and statistical analysis plans are in Supplements 2-7.

Assessments

The coprimary efficacy end points for the studies were achievement at week 16 of (1) at least a 75% reduction from baseline in EASI (EASI 75) and (2) a validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 (clear) or 1 (almost clear) with 2 grade or greater reduction from baseline (vIGA-AD 0/1). Secondary efficacy end points included the achievement at week 16 of a 90% or greater reduction from baseline in EASI (EASI 90), 4-point or greater improvement from baseline in Worst Pruritus Numerical Rating Scale (WP-NRS) score in patients with a WP-NRS score of 4 or greater at baseline, Dermatology Life Quality Index (DLQI; for patients aged ≥16 years) or Children's Dermatology Life Quality Index (CDLQI; for patients aged <16 years) score of 0 or 1 (DLQI 0/1; CDLQI 0/1), a 4-point or greater improvement from baseline in Patient-Oriented Eczema Measure (POEM) in patients with POEM score of 4 or greater at baseline, 12-point or greater improvement from baseline on the Atopic Dermatitis Impact Scale (ADerm-IS) Sleep domain score in patients with ADerm-IS Sleep score of 12 or greater at baseline, and Hospital Anxiety and Depression Scale–Anxiety (HADS-A) score less than 8 and Hospital Anxiety and Depression Scale–Depression (HADS-D) score less than 8 in patients with HADS-A score of 8 or greater or HADS-D score of 8 or greater at baseline.

Safety assessments included treatment-emergent adverse events (TEAEs) (defined as new or worsening adverse events [AEs] after the first study drug dose and within 30 days after the last study drug dose), serious AEs, deaths, AEs leading to discontinuation, and AEs of special interest. Clinically important grade 3 and grade 4 laboratory abnormalities were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.1, and intensity was assessed using CTCAE version 5.0. Independent blinded external committees adjudicated all potential major adverse cardiovascular events (MACEs) and venous thromboembolic events (VTEs).

Statistical Analysis

Data from the 3 studies were analyzed independently. Analyses for all efficacy end points were conducted using the intent-to-treat adolescent population, defined as all adolescents who were randomized at baseline (in the main study and adolescent substudy), after all adolescents completed the 16-week double-blind period. The primary approach for handling missing data due to COVID-19 or other reasons in the analysis of categorical end points was the nonresponder imputation incorporating multiple imputation.[13,14] Patients were considered nonresponders following initiation of rescue medication. For continuous end points, missing data were handled using mixed-effect model repeat measurement. Categorical variables and continuous variables were analyzed using Cochran-Mantel-Haenszel and mixed-effect model repeat measurement methods, respectively. There was no overall type I error control for the analysis of adolescent data; nominal (without multiplicity control) 2-sided *P* values based on a level of significance of .05 are reported. The safety of upadacitinib was assessed by summarizing the frequency of TEAEs in patients who received at least 1 study drug dose during the placebo-controlled period. All statistical analyses were conducted using SAS software, version 9.4 or newer (SAS Institute). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Results

Patients

A total of 552 adolescents (290 female; 262 male) were randomized at 216 clinics in 35 countries between August 13, 2018, and December 23, 2019, in Measure Up 1; between July 27, 2018, and November 10, 2020, in Measure Up 2; and between August 9, 2018, and December 20, 2020, in AD Up. A total of 189, 180, and 183 adolescents with mean (SD) age of 15.4 (1.8), 15.5 (1.7), and 15.3 (1.8) years were randomized in Measure Up 1, Measure Up 2, and AD Up, respectively (eFigure 2 in Supplement 1). Overall, 171 of 184 (92.9%), 177 of 182 (97.3%), and 183 of 186 (98.4%) adolescents randomized to placebo, upadacitinib 15 mg, and upadacitinib 30 mg, respectively, completed the 16-week double-blind period. Key demographics and disease characteristics were generally well balanced between groups and across studies (Table 1).

Efficacy

In Measure Up 1, Measure Up 2, and AD Up, a greater proportion of adolescents achieved EASI 75 at week 16 with upadacitinib 15 mg and upadacitinib 30 mg than with placebo (Figure 1; Table 2; nominal $P < .001$ for all comparisons vs placebo). A greater proportion of adolescents also achieved vIGA-AD 0/1 at week 16 with upadacitinib 15 mg and upadacitinib 30 mg than with placebo (Figure 2; Table 2; nominal $P < .001$ for all comparisons vs placebo). Similar trends demonstrating superiority of upadacitinib over placebo were observed for EASI 90 and the improvement of WP-NRS of 4 or greater at week 16 (Table 2; eFigures 3 and 4 in Supplement 1). The efficacy of upadacitinib in adolescents aged 12 to 17 years was broadly similar to that of adults aged 18 to 75 years for both coprimary and key secondary efficacy end points (eTable 1 in Supplement 1).

A greater proportion of adolescents 16 years and older achieved DLQI 0/1 at week 16 with upadacitinib than with placebo in all studies (Table 2). Similar results were observed for the proportion of adolescents aged 12 to 16 years who achieved CDLQI 0/1 at week 16. The proportion of patients achieving the minimal clinically important difference for the ADerm-IS Sleep subdomain (≥12 points) and POEM (≥4 points) scores was greater for adolescents receiving upadacitinib compared with adolescents receiving placebo. Overall, a greater proportion of adolescents receiving upadacitinib 15 mg or 30 mg had HADS-A score less than 8 and HADS-D score less than 8 at week 16 (among those with HADS-A ≥8 or HADS-D ≥8 at baseline) compared with placebo.

Rescue medication use during the 16-week double-blind period was most frequent in the placebo groups, with a lower rate of rescue medication use in the AD Up study. In Measure Up 1, Measure Up 2, and AD Up, respectively, rescue medication was used by 24 of 61, 27 of 60, and 11 of 63 adolescents (range, 18%-45%) in the placebo group; 5 of 64, 5 of 58, and 4 of 60 adolescents (range, 7%-9%) in the upadacitinib 15-mg group; and 1 of 64, 3 of 62, and 1 of 60 adolescents (range, 2%-5%) in the upadacitinib 30-mg group.

Safety

Overall AE rates in adolescents receiving upadacitinib through week 16 were similar to those reported for adults (eTable 2 in Supplement 1). The rate of serious AEs and AEs leading to discontinuation was low (eTable 3 in Supplement 1) and similar between placebo and upadacitinib 15 mg across the studies (Table 3). There were no serious AEs with upadacitinib 30 mg.

The most common TEAEs in adolescents receiving upadacitinib were acne, headache, upper respiratory tract infection, creatine phosphokinase (CPK) level elevations, and nasopharyngitis (Table 3). Median (range) time to onset of acne among upadacitinib-treated patients was approximately 50 days (upadaci-

tinib 30 mg: 51.5 [11-103] days; upadacitinib 15 mg: 47.5 [1-102] days) (eTable 4 in Supplement 1). Acne was limited to the face and trunk, presenting mostly as comedones, inflammatory papules, and pustules. Acne AEs were almost all mild or moderate (grade 1 or 2), and all were nonserious; only 1 patient discontinued study drug due to moderate acne. Oral medication (retinoid or tetracycline) was used to treat acne in 2 adolescents receiving upadacitinib 15 mg, and topical therapy was used to treat acne in approximately half of the adolescents receiving upadacitinib.

Overall, AEs of special interest were reported infrequently. One patient receiving placebo had a serious infection of grade 3 subcutaneous abscess and cellulitis, and 1 patient receiving upadacitinib 15 mg had a serious infection of grade 3 impetigo (hospitalization on study day 82; patient withdrew consent). Herpes zoster was reported in the upadacitinib groups only in France, Italy, and Croatia (1 case with upadacitinib 15 mg and 3 cases with upadacitinib 30 mg); 2 patients had prior chickenpox/primary varicella infection, and no patients had prior varicella zoster virus (chickenpox) vaccination. Herpes zoster events generally involved 1 to 2 dermatomes and rarely led to treatment discontinuation. The 4 herpes zoster events occurred on days 26, 32, 58, and 82 after the first upadacitinib dose; 2 of these events were ophthalmic herpes zoster occurring in the same patient and led to treatment discontinuation. No opportunistic infections, active tuberculosis, malignant neoplasms (including nonmelanoma skin cancer), or any adjudicated MACEs, VTEs, or events of gastrointestinal perforation were reported in adolescents.

Laboratory-related AEs were generally mild or moderate and rarely led to treatment discontinuation during the 16-week double-blind period; 2 events (grade 1 CPK elevation and grade 3 elevation of liver enzymes) prompted premature discontinuation. Time to onset of these laboratory abnormalities ranged from 1 to 99 days after starting study drug. Almost all events resolved or returned to normal levels with or without temporary treatment interruption. Grade 3 or greater CPK elevations occurred in 4% and 5% of adolescents in the upadacitinib 15-mg and 30-mg groups, respectively, compared with 1% in the placebo group; 5, 4, and 1 adolescent(s) had grade 4 CPK elevations in the upadacitinib 15-mg group, upadacitinib 30-mg group, and placebo group, respectively (eTable 5 in Supplement 1). All patients experiencing grade 3 or greater CPK elevations were asymptomatic. No event of rhabdomyolysis was observed. Grade 3 or greater liver enzyme or creatinine elevations were infrequent and did not occur in more than 1 patient in any treatment group. There was a higher rate of neutropenia in the upadacitinib 30-mg group, with 6 patients (3%) experiencing grade 3 reductions in neutrophil counts, compared with 1 patient and no patients in the upadacitinib 15-mg and placebo groups, respectively. Only 1 patient receiving upadacitinib 30 mg experienced grade 3 or greater thrombocytopenia. There were no cases of grade 3 or greater anemia.

Discussion

Overall, across the 3 randomized clinical trials, upadacitinib 15 mg and 30 mg resulted in superior efficacy than placebo for all efficacy end points at week 16 in adolescents aged 12 to 17 years, with a greater proportion of adolescents receiving upadacitinib achieving EASI 75, EASI 90, vIGA-AD 0/1, and WP-NRS 4 or greater improvement compared with placebo. These results for skin clearance and itch reduction in adolescents were consistent with those observed in adults. The studies were not designed to assess statistical differences between the 2 upadacitinib dose groups, although numerically higher efficacy was observed with the higher dose.

Nominal *P* values for quality of life, as measured by the proportion of patients achieving DLQI 0/1 or CDLQI 0/1, did not reach statistical significance for both upadacitinib doses across the studies, likely because the sample size was split between 2 assessments, as neither are validated for the entire adolescent age range studied and the very high bar set for the analysis of these end points. However, a numerically larger proportion of adolescents receiving upadacitinib achieved these thresholds than did patients receiving placebo. The proportion of patients without anxiety and depression among adolescents with HADS-A or HADS-D score of 8 or higher at baseline (roughly half of the study population) was also numerically greater with upadacitinib than with placebo across the studies. Sleep was improved compared with placebo for both upadacitinib doses across the studies. These patient-reported outcomes in adolescents were also similar to those reported for the overall population, demonstrating a consistency across age groups.

The safety profile of upadacitinib in adolescents aged 12 to 17 years was similar to that seen in adults aged 18 to 75 years. During the phase 3 studies, the most common AE in either adolescents or adults was acne. In a separate analysis of 2583 patients (adults and adolescents) included in the main portion of the phase 3 studies, acne was mild or moderate in all but 1 case (severe acne involving >30% body surface area in an adult), and 2 adults discontinued upadacitinib due to moderate acne.[13,15] Acne was readily manageable with no intervention needed for 44.2% of patients receiving upadacitinib.[15] Most patients who required treatment used topical therapies, including antibiotics, benzoyl peroxide, or retinoids. The incidence of acne was highest among adolescents aged 15 to 17 years and adults 40 years and older.[15] Based on a matched cohort study, the incidence of acne is higher in adolescents with AD compared with adults with AD, but this difference was not apparent in patients receiving upadacitinib.[16] Among adolescents in this report, all acne AEs were mild or moderate, with 1 patient discontinuing upadacitinib 30 mg due to moderate acne.

No malignant neoplasms, MACEs, VTEs, or gastrointestinal perforations were reported in adolescents receiving upadacitinib. Similar to that observed in adults, there was a dose-dependent increased incidence of CPK elevations in adolescents receiving upadacitinib. These CPK elevations were generally asymptomatic and did not lead to treatment discontinuation. Two male adolescents receiving upadacitinib (1 in each dose group) had severely elevated CPK levels greater than 40 000 U/L without physical symptoms, following vigorous physical activity. Neither occurrence was considered a serious AE or resulted in treatment discontinuation. Given that adolescents are generally more physically active than adults, patients receiving upadacitinib were encouraged to properly hydrate during and after exercise. As expected, herpes zoster was reported less frequently in adolescents compared with adults. There was also a dose-dependent increase in the incidence of neutropenia in adolescents, which is a known risk with upadacitinib. However, no apparent association between neutropenia and infections was observed.

Limitations

This analysis has several limitations. The cutoff for the analyses was when the last patient reached 16 weeks of treatment; thus, many had not yet completed 52 weeks of exposure, leading to an inadequate number to characterize the long-term safety profile. Even the number of adolescents who completed 16 weeks is relatively small, limiting full characterization of the safety and efficacy profile of upadacitinib in adolescents. Still, the consistency of the results with the overall population across these studies is encouraging, and the number of adolescents reported in this analysis is larger than those in the recent dupilumab clinical program.[17] Characterization of the safety and efficacy of upadacitinib in adolescents by sex and in younger vs older adolescents was similarly constrained. The study was further limited to patients 12 years or older and with body weight 40 kg or greater; therefore, the safety and efficacy of

upadacitinib in patients younger than 12 years or with body weight less than 40 kg remain unknown, and upadacitinib has not been approved in these populations. Finally, patients with a history of exposure to other Janus kinase inhibitors or dupilumab were excluded; consequently, these results are not able to establish the efficacy of upadacitinib in adolescents who have been treated with those therapies.

Conclusions

In this analysis of 3 randomized clinical trials, treatment of moderate-to-severe AD in adolescents with upadacitinib was effective and generally well tolerated, with an overall efficacy and safety profile similar to that observed in adults, and patient-reported outcomes indicated an overall better health-related quality of life compared with placebo. These results support a favorable benefit-risk profile for upadacitinib treatment in adolescents with moderate-to-severe AD.

Notes

Supplement 1.

eFigure 1. Study design of Measure Up 1, Measure Up 2, and AD Up.

eFigure 2. Disposition of Adolescents.

eFigure 3. Proportion of Adolescents Achieving EASI 90 Response Over the Double-blind Period.

eFigure 4. Proportion of Adolescents with Worse Pruritus NRS ≥4 (Weekly Average) Improvement From Baseline Over the Double-blind Period.

eTable 1. Summary of Efficacy Endpoints and Patient-reported Outcome Measure Endpoints at Week 16 in Adults Aged 18–75 Years

eTable 2. Summary of Treatment-Emergent Adverse Events in Adults Through Week 16

eTable 3. Treatment-emergent Severe Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation of Study Drug in Adolescents Through Week 16

eTable 4. Characterization of Acne Adverse Events in Adolescents

eTable 5. Grade 3 or 4 Laboratory Elevations in Adolescents During the Double-blind Period

Supplement 2.

Measure Up 1 Trial Protocol

Supplement 3.

Measure Up 2 Trial Protocol

Supplement 4.

AD Up Trial Protocol

Supplement 5.

Measure Up 1 Statistical Analysis Plan

Supplement 6.

Measure Up 2 Statistical Analysis Plan

Supplement 7.

AD Up Statistical Analysis Plan

Supplement 8.

Data Sharing Statement

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Figures and Tables

Table 1.

Demographics and Baseline Characteristics for Adolescents

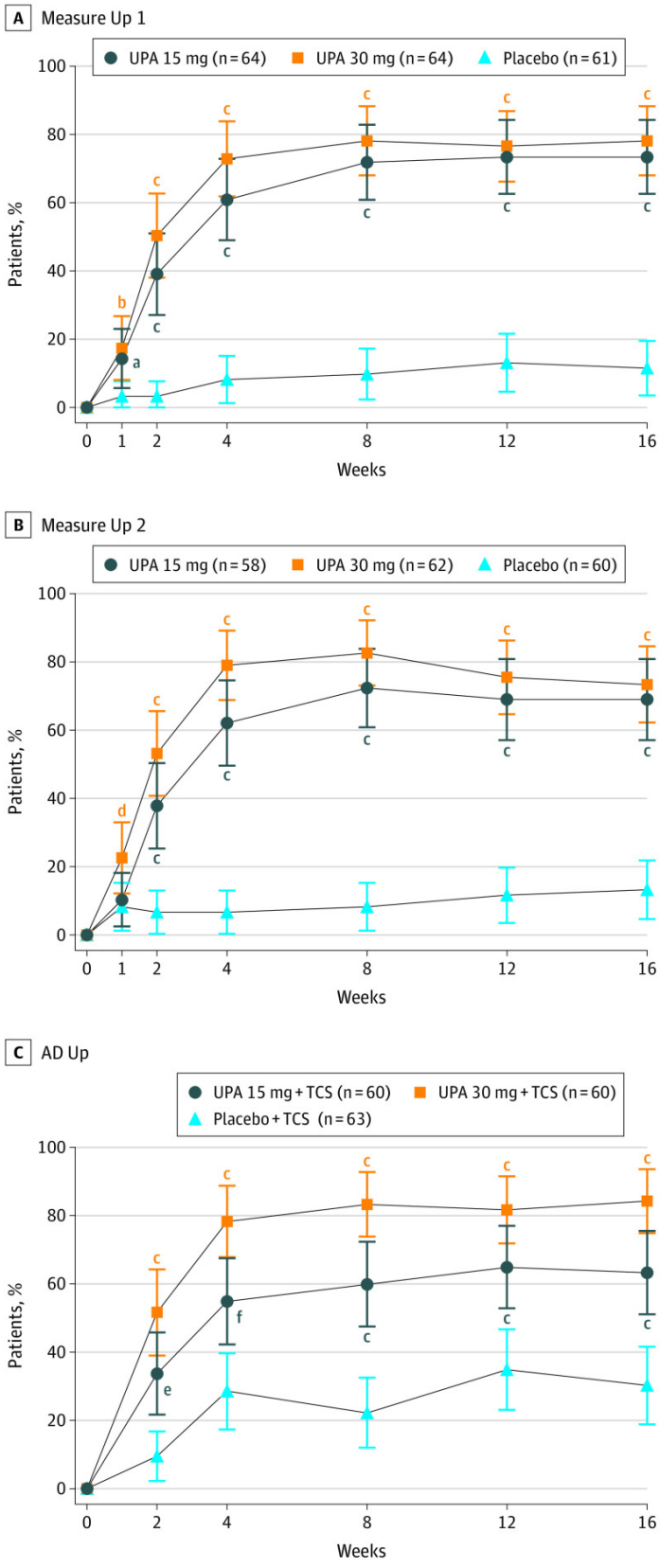
Characteristic	No. (%)								
	Upadacitinib 15 mg			Upadacitinib 30 mg			Placebo		
	Measure Up 1	Measure Up 2	AD Up	Measure Up 1	Measure Up 2	AD Up	Measure Up 1	Measure Up 2	AD Up
No.	64	58	60	64	62	60	61	60	63
Sex									
Female	34 (53)	38 (66)	27 (45)	36 (56)	26 (42)	25 (42)	33 (54)	35 (58)	36 (57)
Male	30 (47)	20 (34)	33 (55)	28 (44)	36 (58)	35 (58)	28 (46)	25 (42)	27 (43)
Age, mean (SD), y	15.5 (2.0)	15.2 (1.8)	15.4 (1.7)	15.7 (1.6)	15.8 (1.7)	15.3 (1.9)	15.1 (1.7)	15.5 (1.7)	15.1 (1.9)
Weight, mean (SD), kg	61.1 (12.2)	60.0 (13.5)	64.1 (18.0)	61.8 (14.8)	64.0 (14.0)	63.9 (18.5)	64.0 (17.0)	66.0 (15.9)	61.4 (16.4)
Race									
Asian	12 (19)	5 (9)	13 (22)	10 (16)	12 (19)	6 (10)	10 (16)	6 (10)	14 (22)
Black	6 (9)	5 (9)	5 (8)	0	3 (5)	6 (10)	6 (10)	7 (12)	5 (8)
White	45 (70)	42 (72)	41 (68)	50 (78)	46 (74)	46 (77)	41 (67)	45 (75)	44 (70)
Other[a]	1 (2)	6 (10)	1 (2)	4 (6)	1 (2)	2 (3)	4 (7)	2 (3)	0
Medical history									
Allergic rhinitis	24 (38)	20 (35)	17 (28)	26 (41)	29 (47)	21 (35)	20 (33)	29 (48)	18 (29)
Asthma	26 (41)	25 (43)	23 (38)	34 (53)	26 (42)	32 (53)	23 (38)	25 (42)	31 (49)
Disease duration, mean (SD), y	12.0 (4.5)	11.2 (4.5)	11.4 (5.1)	12.4 (4.4)	12.1 (4.6)	12.2 (3.9)	11.4 (5.1)	12.2 (4.7)	12.3 (4.3)
% BSA, mean (SD)	48.0 (22.0)	43.7 (22.6)	44.4 (23.4)	42.3 (21.1)	51.4 (24.0)	40.8 (22.5)	49.3 (22.7)	47.6 (22.6)	44.9 (22.6)
Previous systemic therapy[b]	19 (30)	21 (36)	33 (55)	23 (36)	28 (45)	25 (42)	20 (33)	27 (45)	32 (51)
EASI, mean (SD)	30.7 (12.8)	28.0 (12.2)	29.6 (11.7)	27.8 (10.6)	31.2 (14.0)	28.7 (10.1)	29.7 (14.1)	30.1 (13.3)	30.3 (12.1)
vIGA-AD									
3: Moderate	35 (55)	27 (47)	29 (48)	37 (58)	29 (47)	29 (48)	35 (57)	26 (43)	28 (44)
4: Severe	29 (45)	31 (53)	31 (52)	27 (42)	33 (53)	31 (52)	26 (43)	34 (57)	35 (56)
WP-NRS (weekly average), mean (SD)	7.2 (1.6)	7.1 (1.8)	7.0 (1.9)	7.4 (1.6)	6.9 (1.7)	6.9 (1.9)	7.2 (1.8)	7.3 (1.6)	7.3 (1.7)

Abbreviations: ADerm-IS, Atopic Dermatitis Impact Scale; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; POEM, Patient-Oriented Eczema Measure; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS, Worst Pruritus Numerical Rating Scale.

[a] Includes American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, and multiple.

[b] Patients with prior exposure to any Janus kinase inhibitor or dupilumab were excluded from the studies.

Figure 1.



Proportion of Adolescents Achieving EASI 75 Response Over the Double-blind Period

A, Measure Up 1. B, Measure Up 2. C, AD Up. Nominal *P* values are calculated using Cochran-Mantel-Haenszel test with the adjustment of baseline vIGA-AD categories (3; 4). Based on nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19 or nonresponder imputation only if there were no missing data due to COVID-19. EASI 75 indicates at least a 75% reduction in Eczema Area and Severity Index; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

[a]$P = .02$. [b]$P = .007$. [c]$P < .001$. [d]$P = .03$. [e]$P = .001$. [f]$P = .002$.

Table 2.

Proportion of Adolescents Achieving Efficacy and Patient-Reported Outcome Measure End Points at Week 16

Parameter	Measure Up 1			Measure Up 2			AD Up		
	Upadacitinib		Placebo	Upadacitinib		Placebo	Upadacitinib		Placebo
	15 mg	30 mg		15 mg	30 mg		15 mg	30 mg	
EASI									
LS mean change from baseline [95% CI]	−24.2 [−26.3 to −22.1][a]	−24.2 [−26.3 to −22.1][a]	−11.0 [−13.5 to −8.5]	−22.7 [−25.2 to −20.1][a]	−25.0 [−27.6 to −22.5][a]	−11.6 [−14.6 to −8.5]	−23.5 [−25.9 to −21.0][a]	−25.6 [−28.0 to −23.2][a]	−15.2 [−17.7 to −12.7]
No.	60	63	33	53	52	31	55	58	48
EASI 75, No./total No. (%) [95% CI]	47/64 (73) [63 to 84][a]	50/64 (78) [68 to 88][a]	7/61 (12) [4 to 20]	40/58 (69) [57 to 81][a]	46/62 (73) [62 to 85][a]	8/60 (13) [5 to 22]	38/60 (63) [51 to 76][a]	51/60 (84) [75 to 94][a]	19/63 (30) [19 to 42]
EASI 90, No./total No. (%) [95% CI]	30/64 (47) [35 to 59][a]	43/64 (67) [56 to 79][a]	2/61 (3) [0 to 8]	28/58 (48) [35 to 61][a]	38/62 (62) [50 to 74][a]	1/60 (2) [0 to 5]	29/60 (48) [36 to 61][b]	44/60 (74) [62 to 85][a]	13/63 (21) [11 to 31]
vIGA-AD 0/1, No./total No. (%) [95% CI]	29/64 (45) [33 to 58][a]	41/64 (64) [52 to 76][a]	4/61 (7) [0 to 13]	26/58 (45) [32 to 58][a]	37/62 (59) [47 to 72][a]	3/60 (5) [0 to 11]	23/60 (38) [26 to 51][a]	40/60 (67) [56 to 79][a]	7/63 (11) [3 to 19]
WP-NRS									
LS mean change from baseline [95% CI]	−4.2 [−4.9 to −3.6][a]	−4.9 [−5.6 to −4.3][a]	−1.7 [−2.5 to −1.0]	−3.5 [−4.1 to −2.9][a]	−4.6 [−5.2 to −4.0][a]	−0.9 [−1.6 to −0.1]	−4.2 [−4.8 to −3.6][a]	−4.7 [−5.3 to −4.0][a]	−2.4 [−3.1 to −1.8]
No.	50	57	34	49	55	27	50	49	41
WP-NRS ≥4 improvement, No./total No. (%) [95% CI]	30/62 (48) [36 to 61][a]	35/62 (57) [44 to 69][a]	6/60 (10) [2 to 18]	21/55 (38) [25 to 51][a]	34/60 (57) [44 to 69][a]	2/59 (3) [0 to 8]	26/57 (46) [33 to 59][c]	29/56 (52) [39 to 65][a]	13/61 (21) [11 to 32]
DLQI (ages 16 to <18 y)[d]									
LS mean change from baseline [95% CI]	−9.0 [−11.3 to −6.8][e]	−10.0 [−12.1 to −7.9][f]	−4.9 [−8.3 to −1.5]	−7.5 [−10.0 to −5.0]	−9.8 [−11.9 to −7.7][c]	−3.7 [−6.9 to −0.5]	−8.9 [−11.1 to −6.7]	−9.1 [−11.3 to −6.8]	−6.3 [−8.7 to −4.0]
No.	29	32	12	21	28	11	20	20	15
DLQI 0/1, No./total No. (%) [95% CI][g]	6/28 (21) [6 to 37]	10/33 (30) [15 to 46][h]	1/22 (5) [0 to 13]	3/22 (14) [0 to 28]	15/32 (47) [30 to 64][a]	2/26 (8) [0 to 18]	3/25 (12) [0 to 25]	8/20 (40) [19 to 62]	4/24 (17) [2 to 32]
CDLQI (ages 12-15 y)[i]									

Abbreviations: ADerm-IS, Atopic Dermatitis Impact Scale; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; LS, least square; POEM, Patient-Oriented Eczema Measure; WP-NRS, Worst Pruritus Numeric Rating Scale.

[a] $P < .001$ upadacitinib vs placebo.

[b] $P = .001$ upadacitinib vs placebo.

[c] $P = .003$ upadacitinib vs placebo.

[d] The DLQI was administered to patients who were 16 years or older at the time of the screening visit and was administered throughout the duration of the studies.

[e] $P = .046$ upadacitinib vs placebo.

[f] $P = .01$ upadacitinib vs placebo.

[g] For patients with DLQI/CDLQI score greater than 1 at baseline.

[h] $P = .006$ upadacitinib vs placebo.

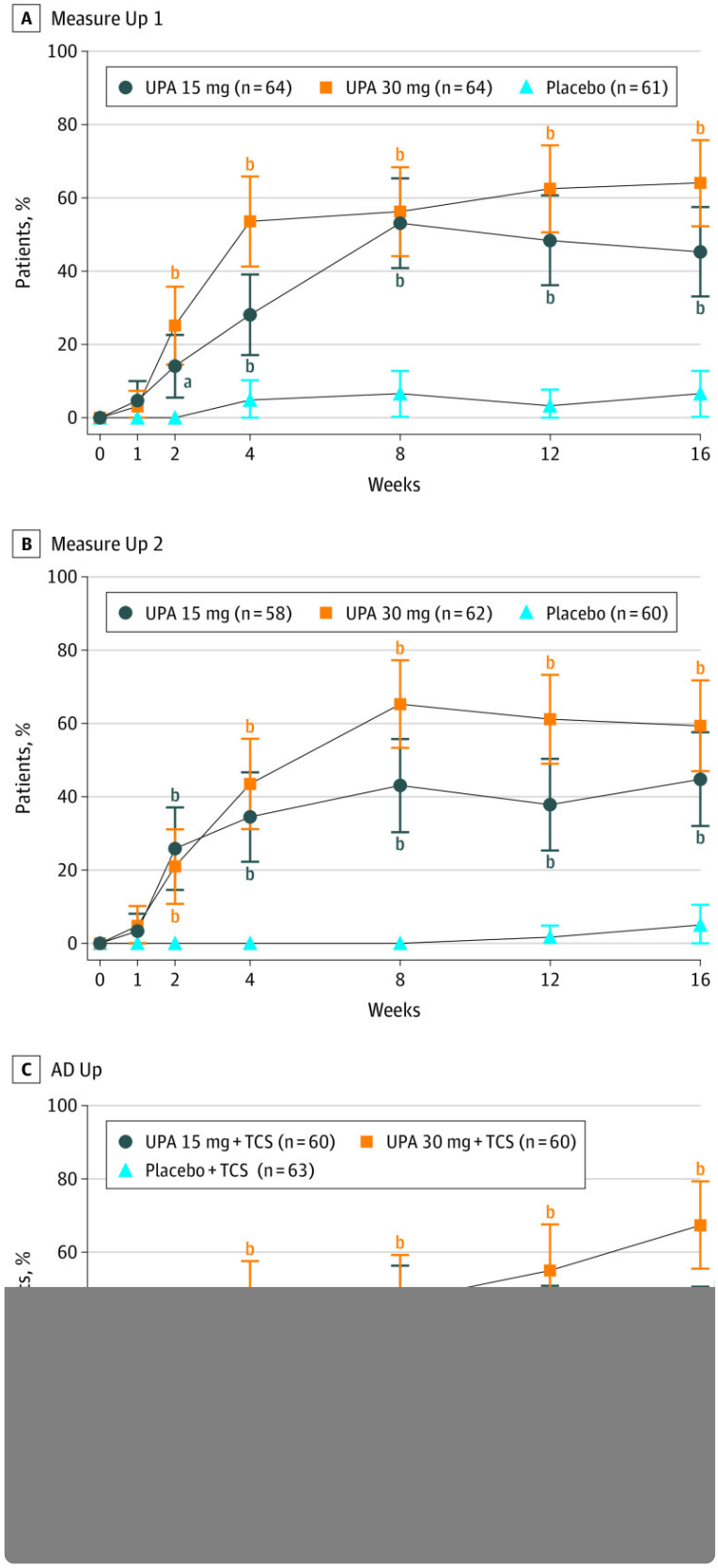
[i] The CDLQI was administered to patients who were younger than 16 years at the time of the screening visit and was administered throughout the duration of the studies.

[j] $P = .03$ upadacitinib vs placebo.

[k] $P = .02$ upadacitinib vs placebo.

[l] For patients with HADS-A or HADS-D score of 8 or greater at baseline.

Figure 2.



Proportion of Adolescents Achieving vIGA-AD Response 0/1 Over the Double-blind Period

A, Measure Up 1. B, Measure Up 2. C, AD Up. Nominal *P* values are calculated using Cochran-Mantel-Haenszel test with the adjustment of baseline vIGA-AD categories (3; 4). Based on nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19 or nonresponder imputation only if there were no missing data due to COVID-19. TCS indicates topical corticosteroids; UPA, upadacitinib; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

[a]$P = .001$. [b]$P < .001$. [c]$P = .004$. [d]$P = .007$.

Table 3.

Summary of Treatment-Emergent Adverse Events in Adolescents Through Week 16

Adverse events	No. (%)								
	Upadacitinib 15 mg			Upadacitinib 30 mg			Placebo		
	Measure Up 1	Measure Up 2	AD Up	Measure Up 1	Measure Up 2	AD Up	Measure Up 1	Measure Up 2	AD Up
No.	64	58	60	64	62	60	61	60	62
All TEAEs	39 (61)	33 (57)	37 (62)	41 (64)	38 (61)	43 (72)	26 (43)	27 (45)	31 (50)
AEs									
Drug-related[a]	21 (33)	12 (21)	14 (23)	20 (31)	15 (24)	22 (37)	9 (15)	3 (5)	9 (15)
Severe	5 (8)	3 (5)	4 (7)	1 (2)	3 (5)	0	1 (2)	2 (3)	0
Serious	1 (2)	2 (3)	1 (2)	0	0	0	1 (2)	3 (5)	0
Drug-related serious[a]	1 (2)	0	0	0	0	0	0	1 (2)	0
Leading to discontinuation	0	2 (3)	1 (2)	1 (2)	0	0	1 (2)	1 (2)	1 (2)
Most commonly reported[b]									
Acne	8 (13)	6 (10)	8 (13)	10 (16)	9 (15)	9 (15)	1 (2)	2 (3)	1 (2)
Headache	5 (8)	3 (5)	5 (8)	4 (6)	5 (8)	4 (7)	2 (3)	2 (3)	4 (7)
Upper respiratory tract infection	5 (8)	6 (10)	1 (2)	8 (13)	3 (5)	4 (7)	5 (8)	1 (2)	1 (2)
CPK elevation	5 (8)	3 (5)	1 (2)	5 (8)	6 (10)	3 (5)	2 (3)	1 (2)	1 (2)
Nasopharyngitis	3 (5)	2 (3)	6 (10)	5 (8)	0	3 (5)	1 (2)	2 (3)	3 (5)
Oropharyngeal pain	2 (3)	4 (7)	1 (2)	0	2 (3)	1 (2)	0	0	1 (2)
Vomiting	0	0	1 (2)	2 (3)	2 (3)	4 (7)	0	0	1 (2)
Pyrexia	1 (2)	2 (3)	0	1 (2)	3 (5)	4 (7)	0	0	0
Diarrhea	1 (2)	1 (2)	1 (2)	2 (3)	1 (2)	3 (5)	0	0	4 (7)
Fatigue	0	3 (5)	1 (2)	0	0	0	0	0	0
Asthma	0	3 (5)	1 (2)	0	2 (3)	1 (2)	0	0	0
AEs of special interest									
Serious infection	1 (2)	0	0	0	0	0	0	1 (2)	0
Opportunistic infection[c]	0	0	0	0	0	0	0	0	1 (2)
Herpes zoster	1 (2)	0	0	2 (3)	0	1 (2)	0	0	0
Active tuberculosis	0	0	0	0	0	0	0	0	0
Malignancy	0	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; TEAE, treatment-emergent adverse event; VTE, venous thromboembolic event.

[a] As assessed by investigator.

[b] Adverse events reported for greater than 5% of patients in any treatment group.

[c] Opportunistic infections excluding tuberculosis and herpes zoster (all opportunistic infections were cases of eczema herpeticum).